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Deprotonative metalation of chlorothiophene with Grignard reagent and catalytic *cis*-2,6-dimethylpiperidine under mild conditions

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Abstract: Deprotonative metalation of chlorothiophene takes place with a catalytic amount of *cis*-2,6-dimethylpiperidine (DMP) and an alkyl Grignard reagent at room temperature for 3 h to give the corresponding thienyl Grignard reagent. Polymerization leading to head-to-tail-type poly(3-substituted thiophene) with the thus metalated chlorothiophene proceeds in the presence of a nickel catalyst bearing *N*-heterocyclic carbene (NHC) ligand. Palladium catalyzed cross-coupling reaction with aryl bromides also gives arylated thiophenes in good to excellent yields whereas the C-Cl bond being intact.

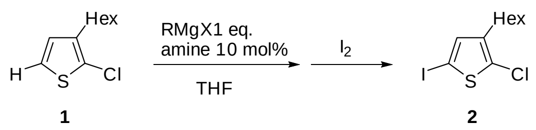
Key words: chlorothiophene, palladium, nickel, cross-coupling, Grignard reagent

Thiophene is an important chemical structure in biologically important compounds[1] as well as organic advanced materials.[2] Transition-metal-catalyzed cross-coupling reaction of organometallic compounds and aryl halides is one of a powerful method forming arylated thiophene motif.[3] Thus, it is important to develop an efficient metalation method toward the use of cross-coupling reaction as well as generation of simple organometallic nucleophile. Knochel and his co-workers developed efficient magnesium amide, which is Knochel-Hauser base, chloromagnesium 2,2,6,6-tetramethylpiperidide lithium chloride salt ($TMPMgCl\cdot LiCl$).[4] They demonstrated deprotonative metalation of several heteroaromatic compounds and following C-C bond formation with various electrophiles under mild conditions. We have also reported recently that metalation of several heteroaromatic compounds occurs with a combined use of a catalytic amount of tetramethylpiperidine (TMP) and a Grignard reagent and following transition metal-catalyzed reactions with the thus obtained thienyl magnesium species lead to the cross-coupled products and several π-conjugated polymers.[5] Although the metalation using the combination of a catalytic amount of TMP and Grignard reagent is effective for several thiophene derivatives, the metalation required 60 °C and longer reaction periods (12-24 h).

Since chlorothiophene is an interesting building block for facile and efficient access to several biologically active compounds,[6] which involve a chlorothiophene moiety, it is intriguing to develop a modification protocol of chlorothiophenes, accordingly. We describe in this communication that efficient metalation of 2-chloro-3-substituted thiophene with a catalytic amount of *cis*-2,6-dimethylpiperidine and Grignard reagent takes place at room temperature and the metalated species is subjected to the cross coupling polymerization and arylation reactions in the presence of a transition metal catalyst.

We first studied metalation of 2-chloro-3-hexylthiophene (**1**) in the presence of ethylmagnesium chloride and a catalytic amount of several amines. Table 1 summarizes the results of metalation, which is confirmed by quenching the generated thiophene-magnesium species with iodine leading to 2-chloro-3-hexyl-5-iodothiophene (**2**). Although the use of dicyclohexylamine (Cy_2NH) as a catalyst showed superior catalytic activity to TMP at 60 °C for 1 h, the reaction at room temperature for 1 h resulted in giving only 44% of **2**. Although DBU was used in the reaction instead of Cy_2NH, no iodinated product was obtained. The reaction with aromatic secondary amine diphenylamine (Ph_2NH) hardly took place at 60 °C for 1 h. Compared with Cy_2NH, less hindered cyclohexylmethylamine was also ineffective. On the other hand, metalation with *cis*-2,6-dimethylpiperidine (DMP) showed superior catalytic activity to afford the iodinated product in 93% conversion and the reaction at room temperature also improved the yield of **2** to 60% after stirring for 1 h. Thus, we surveyed the effect of Grignard reagent at room temperature. The reaction with a more sterically-hindered $^{i}PrMgBr$ resulted to afford **2** in inferior yield (42%) to that with EtMgCl. The addition of LiCl to EtMgCl appeared to slightly improve the yield of **2** to 66%. When the reaction was carried out with 10 mol % of Cy_2NH and EtMgCl at room temperature, the conversion of **1** was found to be 77% after stirring for 3 h (entry 3). By contrast, the use of DMP instead of Cy_2NH induced the metalation much faster (94% conversion after 3 h) suggesting that following transition metal-catalyzed reactions after the metalation with DMP can be carried out under such conditions.

Table 1 Deprotonative metalation of chlorothiophene **1**[a]

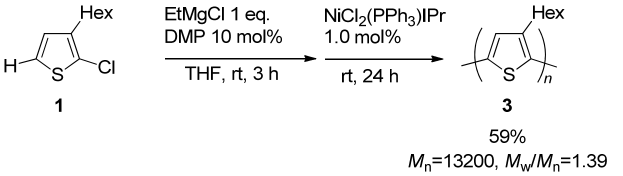


Entry	amine	RMgX	temp. (°C)	Time (h)	conv. (%)[b]
1	Cy_2NH	EtMgCl	60	1	90

2	Cy_2NH	EtMgCl	rt	1	44
3	Cy_2NH	EtMgCl	rt	3	77
4	DBU[c]	EtMgCl	60	1	0
5	Ph_2NH	EtMgCl	60	1	11
6	Cy(Me)NH	EtMgCl	60	1	69
7	DMP[d]	EtMgCl	60	0.5	93
8	DMP	EtMgCl	rt	1	60
9	DMP	^{i}PrMgBr	rt	1	42
10	DMP	EtMgCl	rt	3	94
11	DMP	EtMgCl+LiCl	rt	1	66

[a] The reaction was carried out with 2-chloro-3-hexylthiophene (0.5 mmol), Grignard reagent (0.5 mmol), and amine (0.05 mmol) in 0.5 mL of THF at 60 °C. [b] The conversion was estimated by ^{1}H NMR analysis after quenching the reaction mixture with iodine. [c] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [d] DMP: *cis*-2,6-dimethylpiperidine.

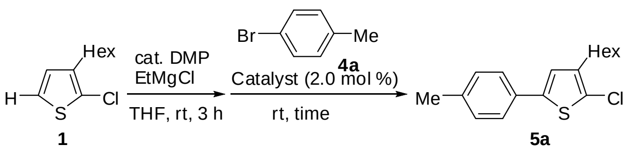
Catalytic generation of 2-chloro-3-hexyl-5-chloromagnesiothiophene was performed with 10 mol % of DMP and EtMgCl at room temperature for 3 h. Polymerization of the resulting solution was examined with 1.0 mol % of $NiCl_2(PPh_3)IPr$ at room temperature for 24 h, which was the standard polymerization conditions employed previously, to afford poly(3-hexylthiophene) (P3HT) (**3**) in 59% isolated yield with M_n of 13200 (M_w/M_n = 1.39) as shown in Scheme 1.[7] Comparing that the deprotonation of **1** with catalytic Et_2NH required a higher reaction temperature and a longer period, the use of DMP allowed the total metalation-polymerization procedures undergoing at room temperature within a shorter deprotonation period.



Scheme 1 Nickel-catalyzed polycondensation of chlorothiophene

We then examined the coupling reaction of 2-chloro-3-hexylthiophene (**1**) with 4-bromotoluene (**4a**) leading to 2-chloro-3-hexyl-5-(4-methylphenyl)thiophene (**5a**). Table 2 summarizes the results. When the coupling reaction of **1** was carried out with 10 mol % of DMP and an equimolar amount of EtMgCl for deprotonation and with 2.0 mol % of $NiCl_2(PPh_3)_2$ at room temperature for 24 h, only a trace amount of coupling product **5a** was obtained. The coupling reaction was performed with several palladium catalysts. Although the coupling reaction was examined in the presence of $PdCl_2(PPh_3)_2$ as a catalyst, we obtained no coupling product **5a** because of the insufficient activity of the palladium catalyst bearing PPh_3 ligands. Drastic improvement was observed when the reaction was carried out in the presence of 2.0 mol % of $PdCl_2dppf$ (dppf: 1,1'-bis(diphenylphosphino)ferrocene) to afford the corresponding coupling product in 52% yield. Similar reaction with $PdCl_2$(d*t*-bpf) (d*t*-bpf: 1,1'-bis(di*tert*-butylphosphino)ferrocene) gave **5a** in only 25% yield. When the catalyst was switched to Pd-PEPPSI-SIPr,[8] which showed excellent catalytic activity in the coupling reaction of 3-hexylthiophene,[9] **5a** was obtained in 49% yield. The metalation with 1.5 equiv.of EtMgCl and the coupling reaction with 1.8 equiv. of 4-bromotoluene in the presence of 2.0 mol % of $PdCl_2dppf$ improved the yield to 69%.

Table 2 Optimization of catalyst for the coupling reaction of **1** with bromoarene **4a**[a]

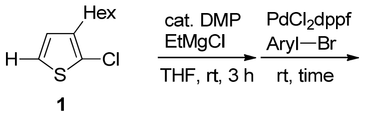


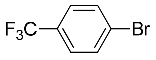
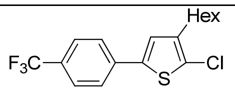
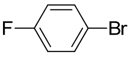
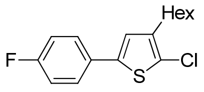
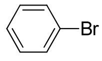
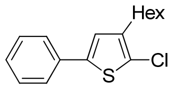
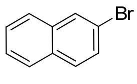
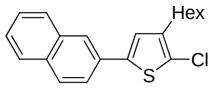
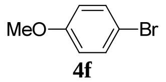
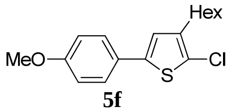
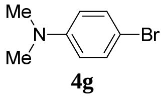
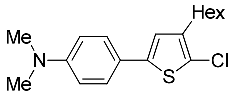
Entry	Catalyst	Time (h)	Yield (%)[b]
1	$NiCl_2(PPh_3)_2$	19	trace
2	$PdCl_2(PPh_3)_2$	17	0
3	$PdCl_2dppf$	15	52
4	$PdCl_2$(d*t*-bpf)	20	25
5	Pd-PEPPSI-SIPr	23	49
6[c]	$PdCl_2dppf$	15.5	69

[a] Unless noted, the reaction was carried out with 0.5 mmol of **1**, 10 mol % of DMP, and 1.0 equiv. of EtMgCl in THF for the metalation, and 2.0 mol % of catalyst and 1.5 equiv. of 4-bromotoluene (**4a**) was employed for the coupling reaction. [b] Isolated yield. [c] The reaction was carried out with 1.5 equiv. of EtMgCl and 1.8 equiv. of **4a**.

The reaction conditions found in Table 2 were applied to the reaction of 2-chloro-3-hexylthiophene (**1**) and several aryl bromides as summarized in Table 3. The reaction with aryl bromide bearing an electron-withdrawing substituent proceeded within relatively shorter reaction period in good to excellent yield. The use of bromobenzene (**4d**) and 2-bromonaphthalene (**4e**) as aryl bromide afforded the corresponding product **5d** and **5e** in 76 and 83 % yields, respectively. On the other hand, the reaction with aryl bromide bearing a more electron-donating group was less effective. The reaction with 4-bromoanisole (**4f**) required relatively long reaction period and the reaction with 4-bromo-*N*,*N*-dimethylaniline (**4g**) gave only 25% yield.[10]

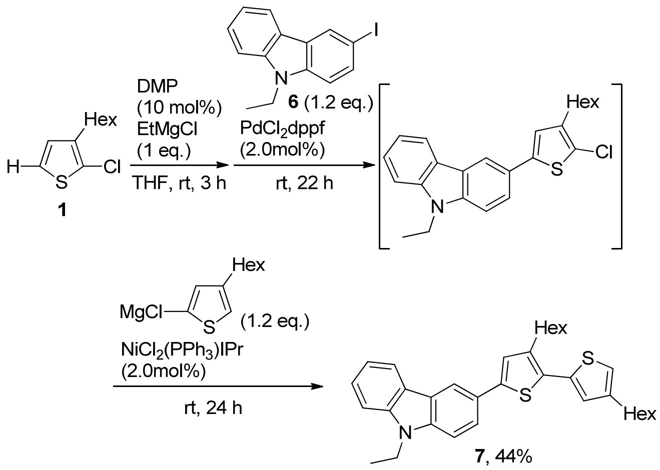
Table 3 Pd-catalyzed coupling reaction of chlorothiophene **1** with aryl bromide[a]



Aryl-Br	Product	Time (h)	Yield (%)[b]
 **4b**	 **5b**	10	51
 **4c**	 **5c**	18	68
 **4d**	 **5d**	14	76
 **4e**	 **5e**	14	83
 **4f**	 **5f**	22	86
 **4g**	 **5g**	20	25

[a] The reaction was carried out with 0.5 mmol of **1**, 10 mol% of DMP, and 1.5 equiv. of EtMgCl in THF for the metalation, and 2.0 mol% of $PdCl_2dppf$ and 1.8 equiv. of aryl bromide was employed for the coupling reaction. [b] Isolated yield.

Thus, selective arylation at the 5-position of chlorothiophene lead to facile synthesis of regioregular head-to-tail-type oligothiophene by one-pot iterative Pd-catalyzed C-H coupling reaction at the 5-position and sequential Ni-catalyzed coupling reaction via C-Cl bond cleavage. Chlorothiophene **1** was first subjected to the reaction of iodocarbazole **6** in THF with 10 mol% of DMP and 1.0 equiv. of EtMgCl at room temperature for 22 h to undergo the coupling reaction. Following addition of 1.2 equiv. of 3-hexyl-5-chloromagnesiothiopehene, which was generated by the selective metalation of 3-hexylthiophene and TMPMgCl·LiCl, and 2.0 mol% of $NiCl_2(PPh_3)IPr$ afforded 2,5-diarylated thiophene **7** in 44% overall yield. The obtained head-to-tail-type bithiophene bearing carbazole moiety is a partial structure of MK-2 dye, which has been employed as dye-sensitized solar cells showing excellent power conversion efficiency.[11] Comparing that the synthesis of such structure has required 3 or 4 steps in our previous report,[5d, 12] the present method improved synthetic efficiency of linear head-to-tail-type oligothiophene bearing carbazole moiety.[13]



Scheme 2. One-pot synthesis of partial structure of MK dye

In conclusion, the combination of catalytic amount of *cis*-2,6-dimethylpiperidine and Grignard reagent is efficient metalating agent of chlorothiophene at the C-H bond. Polycondensation of metalated thiophene took place in the presence of a nickel catalyst to afford corresponding P3HT in good yield. Head-to-tail-type bithiophene bearing carbazole moiety was also synthesized by one-pot iterative Pd-catalyzed C-H arylation reaction and Ni-catalyzed coupling reaction via C-Cl bond cleavage.

Supporting Information for this article is available online at http:// .

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(7) **General procedure for polymerization of chlorothiophene 1:** To a solution of 1.02 M EtMgCl (0.50 mL, 0.5 mmol) in THF were added 2-chloro-3-hexylthiophene (**1**: 0.5 mmol, 101 mg) and *cis*-2,6-dimethylpiperidine (0.05 mmol 6.7 μL) dropwise and the resulting mixture was stirred at room temperature for 3 h. THF (4.5 mL) and $NiCl_2(PPh_3)$IPr (3.9 mg, 0.005 mmol) were successively added and stirring was continued at 25 °C for 24 h. Hydrochloric acid (1.0 M, 20 mL) and methanol (50 mL) were added to form a precipitate. The mixture was filtered and the residue was washed with methanol repeatedly to leave dark purple solid, which was dried under reduced pressure to afford 50 mg of poly(3-hexylthiophene) (**3**). (59% yield). M_n = 13200, M_w/M_n = 1.39.

(8) PEPPSI^{TM}: Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation. SIPr: 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene. See: (a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743. (b) Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383.

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(10) **General procedure for arylation of chlorothiophene**: To a solution of 1.02 M EtMgCl (0.75 mL, 0.75 mmol) in THF were added 2-chloro-3-hexylthiophene (**1**: 0.5 mmol, 101 mg) and *cis*-2,6-dimethylpiperidine (0.05 mmol 6.7 μL) dropwise at room temperature and the resulting mixture was stirred at room temperature for 3 h. THF (2 mL), 4-bromotoluene (**4a**: 0.9 mmol, 0.11 mL), and $PdCl_2$(dppf) (8.2 mg, 0.01 mmol) were successively added and stirring was continued at room temperature for 15.5 h. The reaction mixture was poured into water and the organic materials were extracted with diethyl ether. The organic layer was washed with water twice and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel using hexane as an eluent to afford 101 mg of 2-chloro-3-hexyl-5-(4'-methylphenyl)thiophene (**5a**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 6.9 Hz), 1.25-1.43 (6H, m), 1.50-1.68 (2H, m), 2.35 (3H, s), 2.56 (2H, t, J = 7.7 Hz), 6.96 (1H, s), 7.16 (2H, d, J = 8.1 Hz), 7.39 (2H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.07, 21.13, 22.59, 28.15, 28.93, 29.59, 31.63, 123.02, 123.07, 125.24, 129.56, 131.08, 137.51, 140.21, 140.62; IR (neat) 809, 1041, 1453, 1513, 2856, 2925, 2954; HRMS (DART-ESI+) Calcd for $C_{17}H_{22}{}^{35}ClS$ $[M+H]^+$: 293.1131; found: m/z 293.1131.

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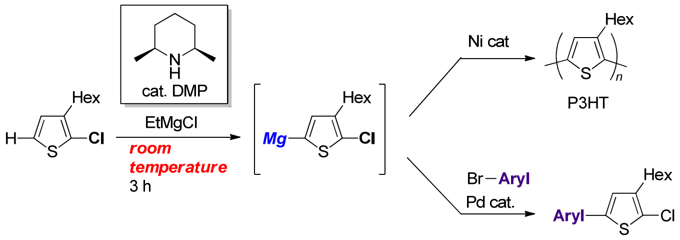

Proton abstraction of chlorothiophene

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